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November 15, 2007

Mail Stop Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Applicant: Mark J. Jaroszeski et al. **Examiner: Jon E. Angell**
Serial No.: 09/939,518 **Art Unit: 1635**
Filing Date: 08/24/2001 **Confirmation No.: 2429**
For: Method of Using Electrical Fields to Facilitate the Entry of Molecules in Cells *In Vivo*
Our Reference: 1372.34

Dear Sir:

Enclosed please find the following:

1. Brief of Appellant having a Certificate of Mailing dated November 15, 2007;
2. Credit Card Payment form in the amount of $255.00, payable to Commissioner for Patents; and.
3. Self-addressed, postage prepaid post card to serve as a receipt for items 1 and 2.

Very respectfully,

SMITH & HOPEN

By: Anton J. Hopen
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AJH/mh
Enclosures

CERTIFICATE OF MAILING
(37 C.F.R. 1.10)

I HEREBY CERTIFY that this Appeal Brief is being deposited with the United States Postal Service as "Express Mail Post Office to Addressee" Mailing Label No. EV928125994US, addressed to: Mail Stop Appeal Brief - Patents, Commissioner for Patents, P.O. Box 1450 Alexandria, VA 22313-1450 on. November 15, 2007.

Date: **November 15, 2007**

Muriel Hartwig

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS AND INTERFERENCES

Serial No.	:	09/939,518	Confirmation No. 2429
Applicants	:	Mark J. Jaroszeski et al.	
Filed	:	08/24/2001	
T.C./A.U.	:	1635	
Examiner	:	Jon E. Angell	
Docket No.	:	1372.34	
Customer No.	:	21,901	
For	:	Method of Using Electrical Fields to Facilitate the Entry of Molecules in Cells *In Vivo*	

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

BRIEF OF APPELANT

Sir/Madam:

In furtherance of its appeal from the Final Rejection mailed 14 June 2007, Applicant hereby submits its Appeal Brief.

TABLE OF CONTENTS

1. REAL PARTY IN INTEREST

The real party in interest is the University of South Florida, the assignee of record, which is a state university, organized under the laws of the State of Florida, as evidenced by the assignment set forth at Reel 012538, Frame 0911.

2. RELATED APPEALS AND INTERFERENCES

There are no appeals, judicial proceedings or interferences known to the appellant, appellant's legal representative, or assignee which will directly affect, or be directly affected by, or have a bearing on the Board's decision in the pending appeal.

3. STATUS OF CLAIMS

Canceled claims:	3-5, 7, 9, 11-20, 23 and 29-52
Withdrawn claims:	None
Rejected claims:	1-2, 6, 8, 10, 21-22 and 24-28
Claims under appeal:	1-2, 6, 8, 10, 21-22 and 24-28

4. STATUS OF AMENDMENTS

No amendments have been made subsequent to the Office's final rejection on 14 June 2007.

5. SUMMARY OF CLAIMED SUBJECT MATTER

Citations to the specification are by page and paragraph number. A concise explanation of the invention defined in the claims involved in this appeal is provided below.

The present invention relates to the electroporation of cells to facilitate the entry of a desired molecule into the interior of a cell or cells in a target tissue. Most therapeutic molecules require delivery to the interior of a cell to effect the desired response. This does not present a problem where the compounds can passively diffuse across the cell membrane or with compounds that are actively taken up by the cell. However, it is frequently the case that one wishes to enhance the delivery of molecules that enter the cell in less than optimal quantities. Similarly, one may wish to make possible the delivery of molecules to the cell's interior when one is working with a compound that is excluded entirely from entry to the interior of the cell. Numerous techniques have been developed to overcome these problems and facilitate the entry of a desired molecule into the interior of the cell or cells, be it in a patient, a test subject or tissue, or in cell culture. One such technique is electroporation.

Electroporation uses electric fields to facilitate the passage of molecules from the extracellular space to the intracellular space. The current understanding of electroporation is that exposure of cells to intense electric fields for brief periods of time temporarily destabilizes membranes. The effect has been described as the dielectric breakdown due to an induced transmembrane potential. The terms "electroporation," or "electropermeabilization," have been applied to the phenomenon because it was observed that molecules that do not normally pass through the membrane gain intracellular access after application of the electric field. The porated state is temporary. Cells typically remain in the destabilized state for a few minutes after the cessation of the field.

The current state of the art uses high electric field strengths to effect the membrane change and requires pulse durations that are very brief. These high field strengths can be from in excess of 100 V/cm to 5000 V/cm. However, as observed by the present inventors, the relationship between the field strength and the pulse duration is critical in effecting the electroporation of cells while avoiding deleterious effects. The present invention is based upon the inventor's discovery that, by using a longer pulse duration, the field strength needed to effect facilitation of molecular delivery may be significantly lowered. As a result, fewer deleterious effects of the procedure are experienced, since the electric field imposition is more a function of time than field strength.

In performing the method, a molecule which one desires to deliver to the interior of a cell or cells is introduced into the target tissue containing the cell. Next, a substantially continuous, low-level electric field is applied to the target tissue. The low-level field is applied for a duration that is sufficient to effect a change in porosity or permeability in the cell or cells of the target tissue. The desired molecule can then pass from the extracellular space to the intracellular space via the resultant permeabilized membrane. The duration of the pulse can be up to 20 minutes when combined with the substantially continuous, low-level electric field.

The essence of the present invention, as articulated in Claim 1, lies in providing a method for facilitating the delivery of a desired molecule into a target tissue. In this method a molecule is introduced into a target tissue having a cell [page 7, lines 12-17; page 8, line 12]. An electric field is then applied to the target tissue [page 8, lines 13-15]. The application of the electric field uses single continuous electric fields having a duration from 200 ms [page 9, table 3 and line 23] to 20 minutes [page 6, line 8]. The application of the electric field then effects a change in porosity of the cell of the target tissue, thus facilitating the entry of a desired molecule into an interior of the cell [page 8, table 2; page 9, lines 1-7; page 9, table 3; page 9, line 21 through page 10, line 3].

Reference to the specification by page and line number for each independent claim:

Claim 1. A method for facilitating the delivery of a desired molecule into a target tissue consisting essentially of the steps of:

introducing a molecule into a target tissue comprising a cell [page 7, lines 12-17; page 8, line 12];

applying an electric field to the target tissue [page 8, lines 13-15], the application of the electric field consisting of a single continuous electric field [page 6, lines 7-8] in the range of 1mV/cm to 200V/cm [page 6, line 7] applied for a duration of 200ms [page 9, table 3 and line 23] to 20 minutes [page 6, line 8]; and

effecting a change in porosity of the cell of the target tissue in response to the application of the electric field, the change in porosity sufficient to facilitate

entry of a desired molecule into an interior of the cell [page 8, table 2; page 9, lines 1-7; page 9, table 3; page 9, line 21 through page 10, line 3].

Claim 21. A method for facilitating the delivery of a desired molecule into a target tissue comprising the steps of:

introducing a molecule into a target tissue comprising a cell [page 7, lines 12-17; page 8, line 12]; and

applying a continuous electric field [page 6, lines 7-8] in the range of 1mV/cm to 200V/cm [page 6, line 7] to the target tissue for a duration of 200ms [page 9, table 3 and line 23] to 20 minutes [page 6, line 8] to effect a change in porosity of the cell of the target tissue sufficient to facilitate entry of a desired molecule into an interior of the cell [page 8, table 2; page 9, lines 1-7; page 9, table 3; page 9, line 21 through page 10, line 3].

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether the Office erred in rejecting claims 1-2, 6, 8, 10, 21-22 and 24-28 under 35 U.S.C §102(e) as being anticipated by U.S. Patent No. 6,678, 558 B1 to Dimmer *et al.*

7. ARGUMENT

Claims 1-2, 6, 8, 10, 21-22 and 24-28 stand rejected by the Office as allegedly being anticipated under 35 U.S.C § 102(e) by U.S. Patent No. 6,678,558 B1 to Dimmer et al. ("Dimmer"). Applicant respectfully submits that Dimmer does not anticipate claims 1-2, 6, 8, 10, 21-22 and 24-28, because Dimmer, contrary to the interpretations of the teachings of Dimmer and assertions by the Office, does not teach each element of the claim under consideration. It is therefore requested that, upon review, the rejection of the claims of the present application be reversed and the application allowed to proceed to issuance.

The claims are generally directed at a method for facilitating the delivery of a desired molecule into a target tissue. Claim 1 is exemplary. The method of claim 1 includes the steps of introducing a molecule to the target tissue and applying a continuous low-level electric field. The continuous, low-level field is applied in the range of 1 mV/cm to 200 V/cm to the target tissue for a duration of about 200ms to 20 minutes. The continuous low-level electric field effects a change in porosity of the cell of the target tissue sufficient to facilitate entry of a desired molecule into an interior of the cell.

Dimmer does not anticipate the claimed subject matter because Dimmer does not teach each element of the claim under consideration. It is well-settled that "[a]nticipation requires the disclosure in a single prior art reference of each element of the claim under consideration." [1, 2] To find anticipation the identical invention must be shown in as complete detail as is contained in the claim with the elements arranged as required by the claim.[3] Dimmer does not teach applying a continuous low-level electric field to the target tissue for a duration of about 200ms to 20 minutes. Instead, Dimmer teaches that patient discomfort associated with electroporation treatment can be accomplished by increasing the frequency of pulses (i.e. decreasing the duration) within an electroporation signal. Pulse frequency is inversely related to pulse

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[1] W.L. Gore and Assoc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303, 313 (Fed. Cir. 1983) (citing Soundscriber Corp. v. United States, 360 F.2d 954, 960, 148 USPQ 298, 301 (Ct. Cl.), *adopted*, 149 USPQ 640 (Ct. Cl. 1966)), *cert. denied*, 469 U.S. 851 (1984); See also Carella v. Starlight Archery, 804 F.2d 135, 138, 231 USPQ 644, 646 (Fed. Cir.), modified on reh'g., 1 USPQ 2d 1209 (Fed. Cir. 1986). RCA Corp. v. Applied Digital Data Sys., Inc., 730 F.2d 1440, 1444, 221 USPQ 385, 388 (Fed. Cir. 1984).

[2] See also MPEP 2131 providing "A claim is anticipated only if each and every element as set forth n the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). ...The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The elements must be arranged as required by the claim, but this is not an *ipsissimis verbis* test, i.e., identity of terminology is not required. *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990).

[3] Id.

duration. Dimmer states that "pulse frequency will preferably have a duration of less than about 5μs." [4] Dimmer does not teach or advocate a pulse duration in excess of 50μs to be used to effect the electroporation of a cell.[5]

Dimmer generally relates "to the use of electric pulses to increase the permeability of cells." [6] More particularly, Dimmer is concerned with the issue that "the electrical signals which are typically used for electroporation cause considerable discomfort" to a patient undergoing treatment.[7] Dimmer therefore teaches methodologies aimed at reducing the discomfort in the patient associated with electroporation treatments. Dimmer advocates an increase in the frequency of the electroporation signal to reduce the discomfort to the patient.[8] Dimmers' teachings are based upon their belief "that strong low frequency component in the monopolar square wave form is responsible for a large portion of the patient discomfort associated with the monopolar square wave form." [9] Dimmer therefore advocates an electroporation signal of reduced frequency.

Dimmer further specifies that "[t]he frequency refers to the frequency of pulses within an electroporation signal." [10] The following formula is provided at column 9, line 59:

Frequency = 1/(First polarity duration + Second polarity duration)

Thus, according to the formula, the frequency is inversely related to the pulse duration. Therefore, the increased frequencies (as advocated by Dimmer to reduce patient discomfort) are to be achieved through reductions in the pulse duration. In other words, according to Dimmer, "as the frequency of electroporation signals ... increases, the patients have increased tolerance to the induced electric field." [11]

Clearly, Dimmer is advocating the use of pulse duration of increasingly short duration to increase the frequency, thereby effecting a reduced discomfort. At column 10, lines 11 through 19 Dimmer states:

> Equation 1 illustrates that increased frequency is associated with a reduced pulse duration. Therapeutic electrical signals according to the present invention preferably ***have a pulse duration of less than about 50 μs***, more preferably have a pulse duration of less than about 12.5 μs and most preferably a pulse duration of less than about 5 μs. In one embodiment of the invention, the pulse duration is about 80 ns-50 μs and in another embodiment of the invention the pulse duration is about 2 μs– 50 μs. (emphasis added)

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[4] U.S. Patent No. 6,678,558 B1 at column 10, line 16.
[5] See for example at column 10, line 14.
[6] U.S. Patent No. 6,678,558 B1 at column 1, line 13.
[7] U.S. Patent No. 6,678,558 B1 at column 2, line 1s 50-52
[8] U.S. Patent No. 6,678,558 B1 at column 9, line 55.
[9] U.S. Patent No. 6,678,558 B1 at column 8, lines 2-5.
[10] U.S. Patent No. 6,678,558 B1 at column 9, line 61.
[11] U.S. Patent No. 6,678,558 B1 at column 9, line 66 to column 10, line 2.

Nowhere in Dimmer is it found, taught or advocated to effect the electroporation of a cell with a pulse having a duration in excess of 50μs. In contrast, the independent claims at issue recite a pulse duration of about 200ms to 20 minutes.

Dimmer further advocates an increase in the electric field.[12] Dimmer provides that "[a]s the electric field increases, the total electroporation signal duration can be decreased in order to prevent excessive amounts of energy from being delivered to the treatment site." [13] This is further evidence of Dimmer's teachings towards a reduction in the duration of the pulse.

Dimmer further teaches that a given electroporation treatment can include multiple pulses; in fact as many as 1 million pulses delivered within a 10 second duration. [14]

The Office has taken the position that Dimmer teaches an electroporation pulse duration meeting the limitations of the claims.[15] Applicant respectfully disagrees with this position. It is submitted that Dimmer does not teach the application of an electroporation signal to effect a change in porosity of the cell and facilitate entry of the desired molecule where the pulse duration is in the range of 200 ms to 20 minutes.

In support of the Office's position regarding the pulse duration, the Office points to column 10, lines 54-60.[16] To put the cited section in perspective, column 10, lines 51-60 are reproduced below:

> The total electroporation signal duration ***is the sum*** of the first polarity durations and the second polarity durations ***of each electroporation signal included in a single electroporation therapy treatment.*** **The total electroporation signal duration** is preferably less than about 10 seconds, more preferably about 30 μs-10 seconds, even more preferably about 30 μs-1 ms and most preferably about 50 μs-400 ms. When the electroporation signals include pulses, the ***total number of bipolar pulses is preferably 1 to 1,000,000.*** (emphasis added)

The excerpted paragraph indicates that the ***total electrporation signal duration*** is less than 10 seconds and can include up to 1 million pulses. This is not the same as saying that a pulse duration is less than 10 seconds, that a pulse duration is between 50μs and 400ms, or, most importantly, that a pulse duration is 200ms or greater. In fact, it is said that "[t]herapeutic electrical signals according to the present invention preferably ***have a pulse duration of less than about 50 μs***, more preferably have a pulse duration of less than about 12.5 μs and most

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[12] U.S. Patent No. 6,678,558 B1 at column 10, lines 39-47.
[13] U.S. Patent No. 6,678,558 B1 at column 10, line 48.
[14] U.S. Patent No. 6,678,558 B1 at column 10, line 59.
[15] Office Action dated 14 June 2007, pages 2-4.
[16] Office Action dated 14 June 2007, page 3, last two lines.

preferably a pulse duration of less than about 5 μs."[17] A reasonable conclusion based upon the combined statements that "[t]herapeutic electrical signals according to the present invention preferably ***have a pulse duration of less than about 50 μs***,..."[18] and "[t]he total electroporation signal duration is ... most preferably about 50 μs-400 ms."[19] is that the duration of any given pulse would not exceed the upper limit of 50 μs. More importantly, nothing about the excerpted statements allows a conclusion that a pulse duration in excess of 50μs is taught by Dimmer. This is buttressed by the general teachings of Dimmer; namely that patient discomfort can be reduced by increasing the frequency of pulses within an electroporation signal and that the frequency can be increased by reducing the pulse duration.

Further evidence of this can be seen in the series of claims 5 through 9 of Dimmer. This claim series, along with claim 1 from which they depend, is reproduced below:

> 1. A method for, co delivering an agent to a cell comprising:
>
> (a) positioning two or more electrodes relative to the cell such that one or more therapeutic electrical signals can pass between at least two of the electrodes and through the cell; and
>
> (b) passing one or more therapeutic electrical signals between at least two of the electrodes to make an electroporated cell, wherein at least one of therapeutic electrical signals simultaneously comprises an agent movement signal and an electroporation signal, wherein the electroporation signal has a frequency greater than about 10 KHz; and
>
> (c) contacting the electroporated cell with the agent to effect delivery of the agent to the cell.
>
> ...
>
> 5. A method according to claim 1 wherein the therapeutic electrical signal is comprised of 1 to about 1,000,000 pulses.
>
> 6. A method according to claim 5 wherein each pulse has a duration of about 2 to about 50 μs.
>
> 7. A method according to claim 5 wherein the therapeutic electrical signal includes a plurality of pulses having a total pulse duration of less than about 10 seconds.
>
> 8. A method according to claim 5 wherein the therapeutic electrical signal includes a plurality of pulses having a total pulse duration of about 1 ms to about 10 seconds.
>
> 9. A method according to claim 5 wherein the therapeutic electrical signal includes a plurality of pulses having a total pulse duration of about 30 ms to 1 second.

Claim 5 indicates/claims that there can be up to 1 million pulses in a therapeutic electrical signal. Claim 6 indicates/claims the each pulse in a therapeutic electrical signal has a pulse duration of 2 to 50μs. Claim 7 then specifies that there can be a plurality of pulses within

[17] U.S. Patent No. 6,678,558 B1 at column 10, lines 12-16.
[18] U.S. Patent No. 6,678,558 B1 at column 10, lines 12-14.
[19] U.S. Patent No. 6,678,558 B1 at column 10, lines 54-58.

a therapeutic electrical signal, the plurality of pulses leading to a duration of the *therapeutic electrical signal* of less than about 10 seconds. This is not the same thing as a *continuous* electric field (i.e. pulse) having a duration of 200 ms to 20 minutes. Only the sum of the pulse durations in Dimmer exceed 50μs.

In further support of the Office's position, the Office has stated that Dimmer teaches application of an electric field "wherein the duration of the applying step is in the range of 200 ms to 100 sec (claims 2 and 22)..."[20] However, claims 2 and 22 of Dimmer do not address the duration of the applying step, but instead address other matters.

The Office has also pointed to "column 13, lines 7-7-19; column 14, lines 21-23; column 23, lines 1-11; column 24, lines 43-50; column 29, lines 12-15; claims 1, 10, 11, 16, 17, 25" in support of the rejection.[21] None of the cited sections of claims address the electroporation pulse duration.

For the foregoing reasons it is respectfully submitted that Dimmer does not teach a methodologies as claimed in the instant invention. It is therefore respectfully requested that the Office withdraw the rejection of claims 1-5, 7 and 8 under 35 U.S.C § 102(b).

Administration of the Agent Movement Signal of Dimmer Does Not Anticipate Applicant's Method

The Office raised the point of Dimmer's application of an agent movement signal and has asserted that Dimmer's teaching of the agent movement signal anticipates the claimed methods.[22] However, Dimmer's agent movement signal does not meet the claim limitation of "effecting a change in porosity of the cell in the target tissue in response to the application of the electric field, the change in porosity sufficient to facilitate entry of the desired molecule into an interior of the cell" as recited in claim 1. Instead, at column 7, lines 19 through 40 Dimmer states:

> [T]he therapeutic electrical signals include electroporation and/or agent movement signals. ***The electroporation signals serve to temporarily create pores in the cells of the treatment*** **site** 30 without causing permanent cell damage. One or more agents, such as genes and/or drugs, can be delivered to the treatment site 30 before, after or during the application of the therapeutic electrical signals. These agents can enter the cells within a treatment site 30 through the pores created by the electroporation signals.
>
> ***The agent movement signals cause movement of an agent relative to cells.*** Certain agents in suspension are

[20] Office Action dated 14 June 2007, page 3, lines 8-9.
[21] Office Action dated 14 June 2007, page 3, final line to page 4, line 2.
[22] Office Action dated 14 June 2007, page 4, first full paragraph.

> known to move through the suspension in response to application of an electric field. The agent movement signals provides the electric field which provides motion to the agents. This movement is generally in a particular direction relative to the applied field. Due to the size difference between cells and the agent, this movement can drive an agent toward a cell. ***When electroporation signals have created pores in the cell,*** the movement of the agent increases the opportunity for the agent to enter the cell though the opening. As a result, the agent movement signals can increase the efficiency of an electroporation treatment.(emphasis added)

Thus, Dimmer teaches an agent movement signal which moves an agent relative to a cell. However, it is Dimmer's electrporation signal that effects the change in porosity in the cell sufficient to facilitate entry of the desired molecule into the interior of the cell. As indicated above, Dimmer's electroporation signals do not meet the duration limits of the instant application's claims. It is further noted that Dimmer recites ranges of agent movement signal voltage levels and pulse durations at column 14 in lines 21-34. Numerous combinations of voltages and pulse durations would be possible within those ranges. However, Dimmer does not teach a particular combination of duration and voltage within the agent movement signal as being sufficient to effect a change in porosity of the cell. Instead, the change in porosity is effected through the particular combination of the voltage levels and pulse durations selected for the electroporation signal (as for instance taught in column 10 of the Dimmer patent).

In response to this, the Office has asserted that Dimmer's method "would necessarily have the same result as the claimed method."[23] However, as indicated above, numerous combinations of voltages and pulse durations are possible within Dimmer's agent movement signal ranges. Dimmer does not teach a particular combination sufficient to effect the change in porosity. Instead, Dimmer teaches that it is their particular combination selected for the electroporation signal which creates the porosity in the cell.

Application of Electric Pulses Having a Duration Less Than and/or a Field Strength Greater Than Those Claimed Would Affect the Basic and Novel Characteristics of the Invention

The Office has indicated that "Applicants argue that instant claims 1, 21, and 24 are limited to a 'continuous electric field…' and assert that this means a *single* electric pulse in the range and duration indicated."[24] It is not completely clear to Applicant what point that the Office is trying to make on page 5. It appears that a number of issues are being dealt with where they should be separately addressed.

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[23] Office Action dated 14 June 2007 at page 4, first full paragraph.
[24] Office Action dated 14 June 2007 at page 5, first sentence.

A "continuous electric field" or "pulse" would correspond to what Dimmer calls a "therapeutic electrical signal" as in column 10, line 12, or what it would appear that Dimmer calls a "pulse" as in claim 5 and column 10, line 59. It does not appear that this is exactly equal to an "electroporation signal" based upon the fact that Dimmer states that "[w]hen the electroporation signals include pulses, the total number of bipolar pulses is preferably 1 to 1,000,000."[25] Thus, apparently electroporation signal may or may not include pulses. This begs the question, then what is an electroporation signal? Dimmer uses a myriad of terminology that can be, at first pass, confusing. One would not equate a "continuous electric field" or "pulse" with Dimmer's "total electroporation signal duration" or his "therapeutic signal" as each of these can include items such as multiple pulses, agent movement signals, time delays,[26] etc. Similarly, one could not say that some thing of Dimmer employing multiple pulses having a total duration for all of those multiple pulses of say "*x*" seconds could be used to anticipate the limitation that a single pulse has a duration of "*x*" seconds (as in our claims where we specify a range beginning at 200ms.) where each pulse in the multiple pulses is necessarily far shorter than "*x*" seconds (or 200 ms.). However, this appears to be what the Office is saying when the say, "Therefore, the claim is not, necessarily limited to a single electric pulse as asserted by Applicants."[27]

The Office has also indicated that "[s]ince there is no evidence in the specification or claims that the presence of additional electric pulses would materially affect the basic and novel characteristic of the claimed method, the phrase "consisting essentially of" can be construed as equivalent to comprising."[28] The Office's point in making this statement is again not completely clear. It is submitted that additional pulses within the parameters claimed (e.g. continuous electric fields in the range of 1mV/cm to 200 V/cm applied for a duration of 200ms to 20 minutes) would not necessarily materially affect the basic and novel characteristics. However, pulses employing high field strengths and/or short pulse durations could materially affect the basic and novel characteristics. It was indicated in the specification that "the present inventors have discovered that, by using a longer pulse duration, the field strength needed to effect facilitation of molecular delivery may be significantly lowered. As a result, fewer deleterious effects of the procedure are experienced since the electric field imposition is more a

[25] U.S. Patent No. 6,678,558 B1 at column 10, lines 58-60.
[26] U.S. Patent No. 6,678,558 B1 at column 8, lines 34-35.
[27] Office Action dated 14 June 2007 at page 5, middle of page.
[28] Office Action dated 14 June 2007 at page 5, middle of page.

function of time rather than field strength."[29] Thus, for instance, the presence of additional pulses where they are high energy could potentially deleteriously affect the process as indicated in the specification.

Additionally, the issue of meeting the limitation of "a single continuous electric field ...applied for a duration of 200ms to 20 minutes ..." (as in claim 1) or "a continuous electric field ... for a duration of 200 ms. to 20 minutes ..." (as in claim 21) is separate from the issue of issue of the transitional phrase used in claiming and the inclusion or exclusion of the presence of additional elements. More specifically, if a limitation in a claim is not met, the particular preamble employed is of little or no significance.[30] One could not say, "you used 'comprising' language (or 'consisting essentially of' language), and, even though you specify a foot-long hot dog, since you used the transitional phrase 'comprising' I am going to say that this does not exclude anticipation by a pair of 6-inch franks." However, this appears to be what the Office is saying when the say, "Since there is no evidence in the specification or claims that the presence of additional electric pulses would materially affect the basic and novel characteristic of the claimed method, the phrase "consisting essentially of" can be construed as equivalent to comprising. Therefore, the claim is not, necessarily limited to a single electric pulse as asserted by Applicants." [31]

Going back to the hypothetical, if the claim specifies a foot-long hot dog, then there must be found a foot-long hot dog in the applied reference to begin to make a case for anticipation. If the applied reference has both a foot-long hot dog and a pair of six-inch franks, then anticipation may hinge on the particular transitional phrase used. However, it appears that the Office is taking the position that a reference teaching a pair of 6-inch franks, but no foot-long hot dog, anticipates a claim limitation of a foot-long hot dog so long as the transitional phrase can be construed as "comprising." (i.e. the sum of the pulse durations, or total electroporation signal duration, can be used against a claim limitation for the duration of a single pulse if "comprising", or something that can be construed as equivalent to comprising, is used in the claims) Furthermore, a statement that a single hot dog is one foot long, is not the same thing as saying that there is only a single hot dog.

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[29] See specification at page 6, lines 13-17.
[30] See Office Action dated 14 June 2007, the section starting at the paragraph straddling pages 5-6 through the paragraph straddling pages 6-7.
[31] Office Action dated 14 June 2007 at page 5, middle of page.

Lastly, towards the end of the middle paragraph of page 5 the Office discusses claims 21 and 24 with reference to previous points made regarding the "consisting essentially of..." language. However, that "consisting essentially of..." language was found in claim 1. Claim 21 is an independent claim and does not use the "consisting essentially of ..." Claim 24 is dependent upon claim 21. Claim 21, as an independent claim, should be construed separately from claim 1. Limitations from claim 1 should not be imported into other claims not dependent therefrom. As the Office points out on page 5, Claim 21 is not necessarily limited to applying only a single electric pulse, but could also encompass applying a plurality of substantially continuous electric pulses. However, at least one of the plurality of pulses must still meet the limitation of "applying a continuous electric field ...for a duration of 200ms to 20 minutes to effect a change in porosity of the cell ..."

For the reasons indicated above, Dimmer does not teach a method for facilitating the delivery of a desired molecule into a target tissue as claimed in the instant application. It is therefore requested that, upon review, the rejection of the claims of the present application be reversed and the application allowed to proceed to issuance.

8. CLAIMS APPENDIX

Serial No: 09/939,518

Filed: 08/24/2001

Title: Method of Using Electrical Fields to Facilitate the Entry of Molecules in Cells *In Vivo*

CLAIMS PENDING AND UNDER APPEAL

1. A method for facilitating the delivery of a desired molecule into a target tissue consisting essentially of the steps of:

introducing a molecule into a target tissue comprising a cell;

applying an electric field to the target tissue, the application of the electric field consisting of a single continuous electric field in the range of 1mV/cm to 200V/cm applied for a duration of 200ms to 20 minutes; and

effecting a change in porosity of the cell of the target tissue in response to the application of the electric field, the change in porosity sufficient to facilitate entry of a desired molecule into an interior of the cell.

2. The method recited in Claim 1, wherein the duration of the applying step is in a range of 200ms to 100 sec.

Claims 3-6 (Cancelled)

6. The method recited in Claim 1, wherein the electric field comprises a pulse selected from a group of waveforms consisting of square, rectangular, exponentially decaying, exponentially increasing, bipolar, and sinusoidal; waveforms having a nongeometrically characterizable shape; waveforms characterizable by a mathematical function; waveforms characterizable by a mathematical approximation; waveforms with at least one of an AC or a DC offset signal; and waveforms without an AC or a DC offset signal.

7. (Cancelled)

8. The method recited in Claim 1, wherein the introducing step comprises the step selected from a group consisting of syringe injection, jet injection, oral dosing, transdermal delivery, infusion into tissue, and infusion into a blood vessel.

Claim 9 (Cancelled)

10. The method recited in Claim 1, wherein the target tissue is selected from a group consisting of skin, tumor, muscle, blood, blood vessel, brain, lymph, liver, pancreas, bone, colon, cardiac, lung, breast, testes, cornea, prostate, and intestine.

Claims 11-20 (Cancelled)

21. A method for facilitating the delivery of a desired molecule into a target tissue comprising the steps of:

introducing a molecule into a target tissue comprising a cell; and

applying a continuous electric field in the range of 1mV/cm to 200V/cm to the target tissue for a duration of 200ms to 20 minutes to effect a change in porosity of the cell of the target tissue sufficient to facilitate entry of a desired molecule into an interior of the cell.

22. The method recited in Claim 21, wherein the duration of the applying step is in a range of 200ms to 100 sec.

Claim 23 (Cancelled)

24. The method recited in Claim 21, wherein the applying step comprises applying a plurality of substantially continuous electric pulses of between 1mV/cm and 200V/cm to the target tissue, wherein the duration of each substantially continuous electric field is sufficient to effect a change is porosity of the cell of the target tissue sufficient to facilitate entry of a desired molecule into an interior of the cell.

25. The method recited in Claim 21, wherein the electric field comprises a pulse selected from a group of waveforms consisting of square, rectangular, exponentially decaying, exponentially increasing, bipolar, and sinusoidal; waveforms having a

nongeometrically characterizable shape; waveforms characterizable by a mathematical function; waveforms characterizable by a mathematical approximation; waveforms with at least one of an AC or a DC offset signal; and waveforms without an AC or a DC offset signal.

26. The method recited in Claim 25, wherein the electric field comprises a pulse comprising a combination of at least two of the pulses selected from the group of waveforms.

27. The method recited in Claim 21, wherein the introducing step comprises the step selected from a group consisting of syringe injection, jet injection, oral dosing, transdermal delivery, infusion into tissue, and infusion into a blood vessel.

28. The method recited in Claim 21, wherein the target tissue is selected from a group consisting of skin, tumor, muscle, blood, blood vessel, brain, lymph, liver, pancreas, bone, colon, cardiac, lung, breast, testes, cornea, prostate, and intestine.

Claims 29-52 (Cancelled)

9. EVIDENCE APPENDIX

None.

10. RELATED PROCEEDINGS APPENDIX

None.

11. CONCLUSION

Applicant respectfully submits that the rejection of claims 1-2, 6, 8, 10, 21-22 and 24-28 under 35 U.S.C. 102(e) is improper and should be withdrawn. Fairness to Applicant requires reversal of the final rejection; therefore, such reversal is solicited.

Very respectfully,

SMITH & HOPEN, P.A.

By: _____

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CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.10

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Muriel Hartwig